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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,231	01/18/2001	Deborah J. Phippard	3221-US	7382

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 07/22/2003

14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,231	PHIPPARD ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3,5-7,11,18,28,29 and 31* is/are pending in the application.

4a) Of the above claim(s) *31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,3,5-7,11,18,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner and Art Unit related to this application have changed. Please address further correspondence to Richard Schnizer, Art Unit 1635. further correspondence information is given at the end of the Action.

An amendment was received and entered as Paper No. 14 on 4/28/03. claims 2, 4, 10, 12, 13, and 23-25 were canceled as requested.

Claims 1, 3, 5-7, 11, 18, 28, 29, and 31 remain pending. Claim 31 was withdrawn from consideration in Paper No. 10 as being drawn to a non-elected invention. Applicant did not traverse the restriction requirement.

Claims 1, 3, 5-7, 11, 18, 28, and 29 are under consideration in this Office Action.

Priority

This application is filed on 01/18/2001.

Priority claimed to provisional application 60/176,523, filed 01/18/2000.

Oath/Declaration

It does not claim benefit of 60/176,523, filed on 01/18/2000.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3, 6, 7, 11, and 18 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The rejected claims embrace naturally occurring, non-isolated nucleic acid compositions in the which the hand of man is not evident. For the claims read on non-isolated nucleic acids in at least one of the individuals that donated genetic material to form the libraries used to isolate SEQ ID NO:58. Claims 5 and 7 are included because the naturally-occurring nucleic acids can be considered to be labeled with histones, which are fluorescent. Claim 11 is included because, as products of sexual reproduction, all humans and their nucleic acids are recombinant. This rejection can be overcome by limiting the claims to isolated nucleic acids, or by otherwise indicating the involvement of the hand of man in the invention. Applicant should take care not to introduce new matter into the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 5-7, 11, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 5-7, 11, and 18 are indefinite because it is unclear what is intended by "between 90% to 100%". The claim requires a percent identity "between" a given range, rather than *within* a given range. The term "between" in this context requires the definition of two end points of a range. As written, the range of 90% to 100% is set forth

as one end point, and there is no second end point. Because the phrase "between 90% to 100%" sets forth no clear boundaries of any range, one of skill in the art cannot know the metes and bounds of the claims. It is suggested that the word "between" should be deleted.

It is should be noted that the term "exhibiting", in the phrase by "a nucleic acid exhibiting a percentage identity", has been interpreted as closed language. That is, the claims are considered to be drawn to nucleic acids **consisting** of a sequence that is 90-100% identical to SEQ ID NO:58, rather than to nucleic acids **comprising** a sequence that is 90-100% identical to SEQ ID NO:58.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 1, 3, 5-7, 11, 18, 28, and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 and dependents are drawn to the genus of nucleic acids "having a nucleotide sequence selected from the group consisting of SEQ ID NO: 58" and to complements of those nucleic acids. SEQ ID NO:58 is an expressed sequence tag, i.e.

a partial cDNA. The genus of nucleic acids having SEQ ID NO: 58 additionally includes complete cDNAs and genomic clones of the gene from which SEQ ID NO:58 was derived. This genus embraces the species of genomic clones, full length cDNAs, introns exons, promoters, or other sequences that may be physically attached to SEQ ID NO:58. See e.g. paragraphs [0014] "[w]here ESTs are identified as coding for previously identified genes, the full length sequence can be cloned)" and [0017] ("[w]here full length sequences are known or obtained, biochemical assays for the protein product can be designed to generate an assay for OA.)"

Claim 3 and dependents are indefinite such that their scope cannot be determined. For the purpose of this rejection they are considered to be drawn to nucleic acids consisting a sequence that is 90-100% identical to SEQ ID NO:58. The claims recite no functional limitations. SEQ ID NO:58 is 225 bases in length, so the claimed genus embraces sequences comprising SEQ ID NO:58 and an additional 25 bases, such as cDNAs derived from the same gene as SEQ ID NO:58 but which contain 25 more bases of information. Such information could include a portion of an open reading frame, RNA processing signals, or sequences influencing RNA stability. The specification fails to describe any such species. The expressed sequence tag, SEQ ID NO: 58 is the only disclosed species of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" *Vas-Cath Inc. v.*

Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116. In the instant case, while a written description for identifying initial expressed sequence tags (ESTs, page 10, line 19) by comparing three EST libraries of OA cartilage and synovium with two EST libraries from donors without OA. There is no written description of any full length cDNA or genomic clone, or of any associated promoter sequence, or of any chromosomal sequences physically attached to the locus comprising SEQ ID NO:58.

In order to meet the written description requirement for genus claims, one must describe or disclose a number of species that is representative of the genus. However, in this case the genus includes a variety of species comprising sequences such as introns, exons, promoters, and poly A addition signals, that are not included in SEQ ID NO:58. The specification provides no description of these other species, and SEQ ID NO:58 contains no information that would allow one to immediately recognize their structures, so one of skill in the art could not conclude that Applicant was in possession of them at the time the invention was filed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of identifying it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person

skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998).

Enablement

Claims 1, 3, 5-7, 11, 18, 28, and 29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 and dependents are drawn to nucleic acids comprising SEQ ID NO:58, and to the complements of those nucleic acids. Claim 3 and dependents are indefinite such that their scope cannot be determined. For the purpose of this rejection they are considered to be drawn to nucleic acids consisting of sequences that are 90-100% identical to SEQ ID NO:58.

The specification teaches that the claimed nucleic acids can be used to diagnose osteoarthritis (OA), to serve as targets for small molecule drug development, to generate therapeutics directly (i.e. gene therapeutics), and to facilitate cloning the complete gene. See pages 3-8.

Enablement of the use of the claimed polynucleotides as diagnostics for OA, for drug development, or for therapy, depends on the establishment of a relationship between OA and the polynucleotides. SEQ ID NO:58 was identified by data mining of ESTs derived from libraries generated from OA patient tissues and non-OA patient tissues. The specification teaches that SEQ ID NO:58 was "preferentially observed" in

libraries generated from OA patient tissues. See e.g. page 3, lines 1-12. It is unclear what is meant by "preferentially observed", and the specification does not disclose sufficient data for one to determine what "preferentially observed" might mean. As a result, the relationship between OA and SEQ ID NO:58 is unclear. For example, "preferentially observed" could mean that SEQ ID NO:58 was never observed in the non-OA libraries, or it could mean that a SEQ ID NO:58 was simply observed less frequently in the non-OA libraries. No data is presented regarding the relative amounts of SEQ ID NO:58 in OA versus non-OA tissues. This is an important point because, as discussed more fully below, in order to use SEQ ID NO:58 as a diagnostic one must obviously know what level of expression of SEQ ID NO:58 is diagnostic of OA.

The prior art recognized that comparison and analysis of differentially expressed ESTs from disease-related and normal libraries was an effective means of identifying candidate sequences that could be developed as diagnostics. See e.g. Fannon (TIBS (1996) 14(8): 294-298) who taught that "[c]arefully constructed EST databases can be viewed as a statistical sampling of genes expressed in a variety of tissues, disease states and developmental stages." Fannon continues " The database becomes a decision-support tool that helps identify candidates for more rigorous subsequent characterization". See page 295, column 1, first two paragraphs. Fannon indicates that EST-database approaches can be used to identify a **potential** diagnostic sequence, but adds that there are a number of issues associated with the EST-database approach that need further study, including:

-How much sequencing should be performed on each library for a representative sampling of gene expression, and,

-In view of the fact that expression patterns vary among individuals, among library-preparations methods, and in response to external stimuli, how do we determine what is a 'normal' amount of gene expression?

Fannon points out that "[w]ork is needed to quantify how much variation in gene expression may be considered healthy or normal, and at what point the expression pattern shifts to the 'disease' profile." See page 296, column 2, line 18 to page 297, column 2, line 14. Given these teachings, it is apparent that the raw results of EST-data mining in disease versus control tissues can provide one with a starting point on the road to the development of a potential diagnostic, if one can show that the sample is statistically significant, if it is determined that the libraries used contain a representative sample of gene expression, and if one has established the threshold between normal and disease-related expression levels in view of the variability of gene expression levels in various patients and differences in library preparation methods. In the instant case, 3 EST libraries were generated from 6 different OA donors (5 cartilage donors and one synovium donor), and were compared to two libraries generated from 5 non-OA donors (4 cartilage donors and one synovium donor). It is unclear how the comparison was made, how many donors contributed to each library, if the contributions were equal, or if the synovial tissue was represented in each library, and there is no information on the genetic backgrounds of the donors. In view of the small sample size, and the uncertain nature of the library composition, it is extremely unpredictable as to

whether the sample is statistically significant and contains a representative sample of gene expression. Furthermore the specification has not establish what, if any, amount of SEQ ID NO:58 expression correlates with OA, and what amount is indicative of no disease. So, at best one of skill in the art would view SEQ ID NO:58 as a candidate sequence which could possibly be developed into a diagnostic tool after further research to more rigorously establish a true correlation between its expression and OA. However, the specification fails to provide adequate information to allow one of skill in the art to assess critical variables related to the preparation of the libraries and the natural variability in expression among individuals, and the specification provides no guidance with regard to what is the threshold between normal and disease-related expression levels in of any gene in OA.

Similarly, asserted uses including use of the claimed sequences to isolate the full length clone for analysis of the encoded protein, to develop gene-based therapies, and to serve as targets for small molecule drug development also depend on first rigorously establishing a correlation between SEQ ID NO:58 and OA. In view of the forgoing discussion regarding the lack of a sufficiently rigorous correlation between SEQ I DNO:58 and OA, one of skill in the art would have to perform undue experimentation to use the claimed sequences for these purposes as well.

Response to Arguments

Applicant's arguments filed 4/28/03 have been fully considered to the extent that they apply to the rejections above but they are not persuasive.

With respect to the written description rejection, Applicant argues at pages 4 and 5 of the response that the cited case law is not applicable to the instant claims. This is unpersuasive because the claimed genus of nucleic acids clearly embraces sequences which are not described in any way, such as complete cDNAs, genomic clones, exons, introns, and various expression control sequences such as enhancers and promoters. Applicant has failed to provide any evidence or reasoning to support the position that the disclosure of SEQ ID NO:58 constitutes a representative number of species of the claimed genus. For these reasons the rejection is maintained.

With respect to the enablement rejection, Applicant argues that the nucleic acids of the current claims would not hybridize to non-OA targets, and would therefore be useful as diagnostic probes. This argument does not apply to the ground of rejection set forth above, which is based on the unpredictability of using the products of EST data mining of diseased and normal libraries as diagnostics, therapeutics, or targets for drug development, without first rigorously establishing a correlation between the ESTs and the disease.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the

hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Richard Schnizer, Ph.D.